

What is claimed is:

1. A pharmaceutical composition comprising a first dose of a gastrin/cholecystokinin (CCK) receptor ligand, and a second dose of an epithelial growth factor (EGF) receptor ligand, wherein the first and second doses are in a proportion in the composition that is effective for inducing islet neogenesis in a subject in need of islet neogenesis.
2. The composition of claim 1, wherein the gastrin/CCK receptor ligand is a synthetic gastrin derivative.
3. The composition of claim 1, wherein the EGF receptor ligand is a recombinant modified EGF.
4. The composition of claim 1, wherein the gastrin/CCK receptor ligand is a synthetic gastrin derivative having a leucine substituted at position 15, and the EGF receptor ligand is a recombinant modified EGF having a deletion of two C-terminal amino acids and having a neutral amino acid substituted at position 51.
5. The composition of claim 1, wherein the subject in need of islet neogenesis is a patient with diabetes.
6. The composition of claim 5, wherein the diabetes is insulin-dependent diabetes.
7. The composition of claim 5, wherein the diabetes is adult-onset diabetes.
8. The composition of claim 1, wherein an amount of the first dose is at least about equivalent by weight to an amount of the second dose in the composition.
9. The composition of claim 1, wherein the first dose is between about 2-fold and about 100-fold greater by weight than the second dose.
10. The composition of claim 1, wherein the first dose is between about 2-fold and about 10-fold by weight greater than the second dose.
11. The composition of claim 1, wherein the first dose is between about 10-fold and about 100-fold by weight greater than the second dose.

12. The composition of claim 1, wherein the first dose is about 0.1 microgram to about 1.0 microgram per kg body weight of the subject per day.

13. The composition of claim 11, wherein the first dose is about 1.0 microgram to about 10 micrograms per kg body weight of the subject per day.

5 14. The composition of claim 11, wherein the first dose is about 10 micrograms to about 100 micrograms per kg body weight of the subject per day.

15. The composition of claim 11, wherein the first dose is about 100 micrograms to about 10 milligrams per kg body weight of the subject per day.

16. The composition of claim 1, wherein the subject is a mammal.

10 17. The composition of claim 16, wherein the mammal is a rodent or a primate.

18. The composition of claim 1, wherein the subject is a human.

19. The composition of any of claims 12-15, wherein the dose per day is divided into a plurality of administrations per day.

15 20. A pharmaceutical composition comprising a synthetic gastrin derivative and a recombinant modified EGF, wherein the ratio of the gastrin derivative to the recombinant modified EGF is about 60:1.

20 21. A pharmaceutical composition comprising a synthetic gastrin derivative having a leucine substituted at position 15, and a recombinant modified EGF having a deletion of two C-terminal amino acids and a neutral amino acid substituted at position 51, wherein the ratio of the gastrin derivative to the modified EGF is about 60:1.

22. A pharmaceutical composition for islet neogenesis therapy (I.N.T.TM), comprising an effective dose of at least about 1 µg/kg body weight of a modified recombinant EGF and at least about 30 µg/kg body weight of a synthetic gastrin derivative.

25 23. A pharmaceutical composition for I.N.T.TM, comprising an effective dose of at least about 1 µg/kg body weight of a recombinant modified EGF having a deletion of two C-terminal amino acids and having a neutral amino acid substituted at position 51, and at least

about 30 µg/kg body weight of a synthetic gastrin derivative having a leucine substituted at position 15.

24. A method for treating a subject having diabetes, comprising: administering for a duration of treatment a composition having a first effective dose of a gastrin/CCK receptor ligand and a second effective dose of an EGF receptor ligand, the first and second effective doses being suitable for inducing islet neogenesis in a subject in need of islet neogenesis, and causing a period of remission which is at least about four-fold greater than the duration of treatment.

25. The method of claim 24, wherein the composition is effective in increasing blood insulin and reducing blood glucose for the period of remission.

26. The method of claim 24, wherein the composition of the first and second effective doses are mixed and administered as a single injection.

27. The method of claim 24, wherein the composition of the first and second effective doses are mixed and administered as a single subcutaneous injection.

28. The method of claim 24, wherein treatment reduces the dose of exogenous insulin needed to prevent hyperglycemia in an insulin-dependent diabetic.

29. The method of claim 24, wherein the subject is a human, and a duration of treatment is less than about 0.3 percent of an average human life span.

30. The method of claim 29, wherein the duration of treatment is less than about 0.2 percent of the average human life span.

31. The method of claim 30, wherein the duration of treatment is less than about 0.1 percent of the average human life span.

32. The method of claim 24, wherein the subject is a human, and a period of remission is at least about 0.5 percent of an average human life span.

33. The method of claim 24, wherein the period of remission is at least about one percent of an average human life span.

34. The method of claim 24, wherein the period of remission is at least about two percent of an average human life span.

35. The method of claim 24, further comprising repeating administering the composition at a time corresponding to about the end of the period of remission.

5 36. A method for treating a subject having insulin-insufficient diabetes, comprising:

administering a dose of each of a synthetic gastrin derivative and a recombinant modified EGF, for a term of treatment which is shorter in duration than about one percent of an average lifespan of the subject species, the treatment resulting in a remission of the
10 diabetes wherein the subject has increased blood insulin and decreased blood glucose; and repeating administering the composition at a time corresponding to about the end of the remission, thereby treating the subject having insulin-insufficient diabetes.

15 37. A method for treating a subject having insulin-insufficient diabetes, comprising:

administering for a term of treatment which is shorter in duration than about one percent of an average lifespan of the subject species a dose of each of a synthetic gastrin derivative having a leucine substituted at position 15, and a recombinant modified EGF having a deletion of two C-terminus amino acids and a having neutral amino acid substituted
20 at position 51, the treatment resulting in a remission of the diabetes wherein the subject has increased blood insulin and decreased blood glucose; and repeating administering the composition at a time corresponding to about the end of the remission, thereby treating the subject having insulin-insufficient diabetes.

25 38. A method of treating a diabetes patient in need of islet neogenesis, comprising:

administering to the patient a composition comprising a first effective dose of a gastrin/CCK receptor ligand and an a second effective dose of an EGF receptor ligand, the composition being administered according to a dosing schedule of short duration;

30 monitoring the blood glucose level in the patient following administering the composition; and

reiterating administering the composition to the patient when an increase in blood glucose level indicates that the patient is in need of further islet neogenesis, such that the diabetes patient in need of islet neogenesis is treated.

5 39. The method of claim 38, wherein administering the composition causes increased blood insulin and decreased blood glucose.

 40. The method of claim 38, wherein the duration of the dosing schedule is less than about three months.

10 41. The method of claim 40, wherein the duration of the dosing schedule is less than about two months.

 42. The method of claim 41, wherein the duration of the dosing schedule is less than about one month.

15 43. The method of claim 38, wherein monitoring the blood glucose level is less frequent than about three times daily.

 44. The method of claim 43, wherein monitoring the blood glucose level is less frequent than about once daily.

 45. The method of claim 46, wherein monitoring the blood glucose level is less frequent than about once weekly.

20 46. The method of claim 35, wherein monitoring the blood glucose level is self-monitoring by the patient.

 47. The method of claim 38, wherein reiterating administering the composition is less frequent than about once per six months.

25 48. The method of claim 38, wherein reiterating administering the composition is less frequent than about once per year.

 49. The method of claim 38, wherein reiterating administering the composition is less frequent than about once per two years.

50. The method of claim 38, wherein the first effective dose of a gastrin/CCK receptor ligand in the composition is at least about ten-fold greater by weight than the second effective dose of the EGF receptor ligand.

51. A method of treating a diabetes patient in need of islet neogenesis,
comprising:

administering to the patient a composition comprising a synthetic gastrin derivative and a modified recombinant EGF, such that islet neogenesis is initiated and blood glucose is substantially reduced, the composition being administered according to a dosing schedule of less than about two months duration;

monitoring the blood glucose level at intervals of less than about once per day; and
reiterating administering the composition to the patient less frequently than about once per six months.

52. A method of treating a diabetes patient in need of islet neogenesis,
comprising:

administering to the patient a composition comprising a synthetic gastrin derivative having a leucine at position 15, and a recombinant modified EGF having a deletion of two C-terminus amino acids and having a neutral amino acid substituted at position 51, such that islet neogenesis is initiated and blood glucose is substantially reduced, the composition being administered according to a dosing schedule of less than about two months duration;

monitoring the blood glucose level at intervals of less than about once per day; and
reiterating administering the composition to the patient less frequently than about once per six months.

53. A method of reducing exogenous insulin usage in an insulin-dependent diabetic patient, the method comprising:

administering an effective dosage of an I.N.T.TM composition, to induce islet neogenesis; and

reducing the dose of exogenous insulin needed to prevent high blood glucose,
whereby blood glucose is decreased.

54. The method of claim 53, wherein the composition comprises a gastrin/CCK receptor ligand and an EGF receptor ligand.

55. The method of claim 54, wherein the composition comprises the gastrin/CCK receptor ligand in an amount that is at least about 10-fold greater in weight than an amount of the EGF receptor ligand.

56. The method of claim 53, wherein administering the composition is performed according to a schedule less than about three months in duration.

57. The method of claim 56, wherein reducing insulin delivery is initiated after cessation of administering the composition.

58. The method of claim 57, wherein reducing insulin delivery is initiated within the duration of the schedule of administering the composition.

59. The method of claims 57 or 58, wherein insulin delivery after administering the composition is reduced to less than about 70% compared to usage in the diabetic patient before administering the composition.

60. The method of claims 57 or 58, wherein insulin delivery after administering the composition is reduced to less than about 50% compared to usage in the diabetic patient before administering the composition.

61. The method of claims 57 or 58, wherein insulin delivery after administering the composition is reduced to less than about 10% compared to usage in the diabetic patient prior to administering the composition.

62. The method of claims 57 or 58, wherein insulin delivery after administering the composition is reduced to less than about 1% compared to usage in the diabetic patient prior to administering the composition.

63. A method of reducing insulin usage in an insulin-dependent diabetic patient, the method comprising:

administering an effective dosage of a gastrin/CCK receptor ligand and an effective dosage of an EGF receptor ligand in a proportion of at least about 10:1; and

reducing insulin delivering following onset of reduction of blood glucose in the patient.

64. A method of increasing islet neogenesis in a patient, comprising administering
5 over a term of short duration a gastrin/CCK receptor ligand and an EGF receptor ligand, such that islet neogenesis is increased.

65. A kit comprising a gastrin/CCK receptor ligand and an EGF receptor ligand.

66. The kit of claim 65, wherein the gastrin/CCK receptor ligand and the EGF
10 receptor ligand are combined in a single container.

67. The kit of claim 65 or 66, wherein the gastrin/CCK receptor ligand and the EGF receptor ligand are present as unit dosages.

68. The kit of claim 65, further comprising insulin.

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